Remarks

Applicants have carefully considered this Application in connection with the Examiner's Action and respectfully request reconsideration of this Application in view of the following remarks.

The Examiner objected to the disclosure due to improper Markush language in Claim 1. Claim 1 has been amended so that it contains proper Markush language.

I. Rejection under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 1-8 under 35 U.S.C. § 103(a) as being unpatentable over U.S. 2004/0058914 ("Doi"). Applicants respectfully traverse this rejection.

Applicants have discovered that compounds of formula I in Claim 1 can be used to treat urinary incontinence. Applicants claim methods of treating urinary incontinence by administering such compounds and claim the use of such compounds for the treatment of urinary incontinence.

The Examiner states that Doi teaches the administration of the neurokinin receptor antagonist DNK333 (the compound of Claim 7 in the present application) in the treatment of urinary incontinence. (See Office Action, p. 2.) The Examiner further states that the claims of the present application are open to the inclusion of any number of additional therapeutic drugs in the claimed method of treating urinary incontinence. (See Office Action, p. 3.)

However, as set forth in the attached Declaration of Eckhard Weber under 37 C.F.R. § 1.132 (the "Declaration") Doi does not demonstrate that any of the compounds disclosed in Doi are effective to treat urinary incontinence. (See Declaration, paragraph 4). The only experimental data in Doi that purports to demonstrate the effectiveness of

the disclosed compounds in treating urinary incontinence are in Experimental Examples 1 and 2. (See Declaration, paragraph 4).

The model in Experimental Examples 1 and 2 that purportedly tested for the efficacy of a composition with respect to urinary incontinence was based on the treatment of animals under a urethane anesthesia with cyclophosphamide. Instead of testing for the efficacy of a composition with respect to urninary incontinence, the model tested for the efficacy of a composition with respect to increasing bladder capacity. (See Declaration, paragraph 4).

As set forth in the Declaration, cyclophosphamide is known to induce cystitis in rats, and the model used in Doi is a model for cystits, which is an inflammatory condition, and not a model for urinary incontinence. (See Declaration, paragraphs 5 and 6.) (As noted in the Declaration, although it is unclear whether a rat or guinea pig model was used in Doi, cyclophosphamide was used in both Experimental Examples 1 and 2 and would have induced cystitis in the animals that were used, and therefore, the model that was used in Experimental Examples 1 and 2 was a model of cystitis. (See Declaration, footnote 1.))

Urinary incontinence is generally attributed to sphincter incompetence or detrusor muscle overactivity, both of which involve a neuromuscular mechanism, and if inflammation plays a role in urinary incontinence, it is a minor role. (See Declaration, paragraph 6.) The model used in the Doi reference is a model that is not directed towards a neuromuscular mechanism for urinary incontinence and is not a model for urinary incontinence. (See Declaration, paragraph 6).

In contrast to the model used in Doi, an in vivo model of stimulated micturition in conscious guinea pigs and an isolated guinea pig detrusor contractility model were used by the Applicants (see Specification, p. 10, paragraph 2). Guinea pig models were used because of the high homology of guinea pig and human NK receptors. (See Declaration, paragraph 9.) The in vivo model of stimulated micturition (see Example 1 of the Specification) is based on the subcutaneous administration of 5-

hydroxytryptophan (5-HTP), which is a precursor for serotonin, which is a key neurotransmitter of the viscera and triggers neuromuscular detrusor contractions. (See Declaration, paragraph 9.) The other model (see Example 2 of the Specification) is based on the application of substance P, which is the endogenous ligand for NK receptors and also a key neurotransmitter triggering neuromuscular detrusor contractions. (See Declaration, paragraph 9.) Both models used by the Applicants tested DNK333, which is a dual NK_1 and NK_2 antagonist, focused on neuromuscular mechanisms for urinary incontinence, such as a neuromuscular mechanism of detrusor overactivity, and are models for non-inflammatory overactive bladder/urinary incontinence. (It is noted that the Examiner states that in most cases of urinary incontinence, the common pathology involves the detrusor muscle. (See Office Action, p. 3.)) Therefore, the experimental results in the Specification demonstrate preclinical efficacy of the compounds of formula I of present Claim 1 for the treatment of urinary incontinence. (See Declaration, paragraph 9.) This is in stark contrast to Doi which does not provide any experimental evidence demonstrating that any of the compounds disclosed in Doi are effective to treat urinary incontinence. (See Declaration, paragraphs 4 and 10.)

In addition, Doi states:

> The present invention aims at providing a pharmaceutical agent that can be widely applied to diseases such as urinary frequency, urinary incontinence, asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, osteoarthritis, pain, cough, irritable bowel syndrome, emesis, depression, anxiety, manic depression psychosis, schizophrenia and the like. (See paragraph [0009].)

As demonstrated in the Declaration, Doi has not provided any experimental evidence that the compounds disclosed in the Doi reference are effective in treating urinary incontinence. Doi has only provided experimental evidence with respect to the treatment of cystitis. (See Declaration, paragraph 10.) Further, Doi has only provided experimental evidence with respect to combination treatment. (See Declaration, paragraph 10.) As a result, based on the experimental data provided by the Doi reference, one of ordinary skill in the art could not conclude from such experimental

data that a compound according to formula I of present Claim 1 would be effective in the treatment of urinary incontinence. (See Declaration, paragraph 10.)

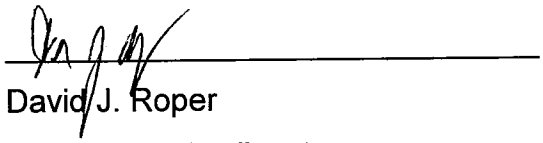
Since Doi does not provide any experimental evidence that its compositions are useful for the treatment of urinary incontinence and a variety of uses of the compositions in Doi are disclosed, the claimed inventions of Applicants are patentable over Doi.

II. Conclusion

In view of the foregoing, Claims 1-8 are in condition for allowance, and Applicants earnestly solicit a Notice of Allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this Application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration to this Reply is respectfully requested.

Respectfully submitted,
Montgomery, McCracken, Walker & Rhoads, LLP



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